IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Jun-Ichi Nezu *et al.*	Art Unit	: 1647
Serial No.	: 10/762,154	Examiner	: Bridget E. Bunner
Filed	: January 21, 2004	Conf. No.	: 4898
Title	: POLYNUCLEOTIDES ENCODING hOCTN1 POLYPEPTIDE		

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Commissioner for Patents
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AMENDED BRIEF ON APPEAL

Appellant is appealing the final rejection of claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 in the Final Office Action dated September 27, 2007, as modified and elaborated in the Advisory Actions respectively dated April 11, 2008, and August 1, 2008. An Amendment after Final was filed on February 25, 2008, and received by the U.S. Patent and Trademark Office on that date. A Notice of Appeal was filed on March 26, 2008, and received by the U.S. Patent and Trademark Office on that date. Appellant filed an Appeal Brief on October 27, 2008, and now presents this Amended Brief on Appeal with a corrected recitation of the Real Party in Interest.

(i) Real Party in Interest

The Real Party in Interest is Chugai Seiyaku Kabushiki Kaisha, the assignee of record, which is also known as Chugai Pharmaceutical Co. Ltd., and which is 60% owned by Roche Pharmholding BV, thereby making it a member of the Roche family of companies owned of record by Roche Holding Ltd.

(ii) Related Appeals and Interferences

There are no prior or pending related appeals, judicial proceedings, or interferences.

(iii) Status of Claims

Claims 1-7, 9, 12, 14, 15, 17, 22, 26 and 28-31 are canceled.

Claims 33-35 are withdrawn.

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Claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 are rejected and under appeal.

(iv) Status of Amendments

The Advisory Action dated August 1, 2008 (henceforth "the Advisory Action") states that, for purposes of appeal, all previously filed amendments have been entered. No amendments are being submitted herewith.

(v) Summary of Claimed Subject Matter

The claims under appeal are directed to (a) isolated nucleic acids encoding an organic cation transporter protein, hOCTN1, and certain variants thereof; (b) vectors and cultured host cells containing the isolated nucleic acids; and (c) methods of producing the encoded polypeptides. Withdrawn method claims 33-35, directed to methods of screening compounds for the ability to be transported by the polypeptide encoded by the nucleic acid of claim 8, are not under appeal; however, they are retained in the application for possible rejoinder, in accordance with MPEP § 821.04, if claim 8 is deemed allowable. Claims 8, 10, 11 and 36 are the independent claims under appeal. As all of the claims are individually addressed in the arguments below, all are summarized here.

Claim 8 is directed to an isolated nucleic acid encoding a polypeptide that includes the sequence of SEQ ID NO:1. SEQ ID NO:1 is the amino acid sequence of a human protein, hOCTN1, discovered by the inventors. Support for independent claim 8 can be found in original claims 5, 8, and 9, as well as in the specification, *e.g.*, at page 6, lines 6-23.

Claim 10 is directed to an isolated nucleic acid encoding a polypeptide that contains the amino acid sequence of SEQ ID NO:1 with one to 30 conservative amino acid substitutions, where the polypeptide is a transporter of an organic cation. Support for independent claim 10 can be found in original claims 10 and 6, as well as in the specification on page 5, lines 12-21, and page 9, lines 1-14.

Claim 11 is directed to an isolated nucleic acid that hybridizes under stringent conditions to a probe, where the sequence of the probe consists of the complement of SEQ ID NO:2, and where the isolated nucleic acid encodes a polypeptide that is a transporter of an organic cation. The stringent conditions include hybridization at 68 °C followed by washing in 2 X SSC/0.1%

SDS for 20 minutes at room temperature and twice in 0.1 X SSC/0.1% SDS for 20 minutes at 50 °C. SEQ ID NO:2 is the sequence of cDNA encoding the hOCTN1 protein of SEQ ID NO:1. Support for independent claim 11 can be found in original claim 11, as well as in the specification, *e.g.,* at page 6, lines 3-5, at page 10, lines 13-31, and at page 11, line 21, to page 12, line 14.

Claim 13 is directed to the nucleic acid of claim 11, wherein the amino acid sequence of the polypeptide comprises SEQ ID NO:1. Claim 11 and its support are summarized above. Claim 13 is supported by original claims 11, 12 and 13, and by the specification, *e.g.,* at page 6, lines 3-11.

Claim 16 is directed to a vector comprising the nucleic acid of claim 8. Claim 8 and its support are described above. Claim 16 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, line 23, and in Example 6.

Claim 18 is directed to a vector comprising the nucleic acid of claim 10. Claim 10 and its support are described above. Claim 18 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, line 23.

Claim 19 is directed to a vector comprising the nucleic acid of claim 11. Claim 11 and its support are described above. Claim 19 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, line 23.

Claim 20 is directed to a vector comprising the nucleic acid of claim 13. Claim 13, in turn, depends from claim 11, which is described above. Claim 13 further limits the nucleic acid of claim 11 to a nucleic acid encoding a polypeptide with an amino acid sequence that includes SEQ ID NO:1. Claim 20 is supported by original claims 11-13 and 20. It is also supported in the specification at, *e.g.,* page 5, line 23.

Claim 21 is directed to a cultured host cell comprising the nucleic acid of claim 8. Claim 8 and its support are described above. Claim 21 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, lines 24-28, and in Example 6.

Claim 23 is directed to a cultured host cell comprising the nucleic acid of claim 10. Claim 10 and its support are described above. Claim 23 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, lines 24-28.

Claim 24 is directed to a cultured host cell comprising the nucleic acid of claim 11. Claim 11 and its support are described above. Claim 24 is an original claim, so provides its own written description. It is also supported in the specification at, *e.g.,* page 5, lines 24-28.

Claim 25 is directed to a cultured host cell comprising the nucleic acid of claim 13. Claim 13, in turn, depends from claim 11, which is described above. Claim 25 is supported by original claims 11, 12, and 25, as well as page 5, lines 17-28, and Example 6.

Claim 27 is directed to a method of producing a polypeptide, the method comprising isolating the polypeptide from the cultured host cell of claim 21. Claim 21, in turn, is drawn to a cultured host cell comprising the nucleic acid of claim 8. Claims 8 and 21 are summarized above. Claims 27 and 21 are both originally filed claims, so provide their own support. They find further support in the specification, *e.g.,* at page 5, lines 26-28; page 7, lines 14-16; and page 12, line 20, to page 13, line 14.

Claim 32 is directed to the nucleic acid of claim 10, further specifying that the sequence of the encoded polypeptide comprises SEQ ID NO:1 with up to 10 conservative amino acid substitutions. Claim 10 and its support are described above. Claim 32 is supported in the specification, *e.g.,* at page 10, lines 4-6.

Claim 36 is directed to an isolated nucleic acid encoding a polypeptide that consists of the sequence of SEQ ID NO:1. Support for claim 36 can be found in the specification, *e.g.*, at page 6, lines 6-11.

(vi) Grounds of Rejection to be Reviewed on Appeal

Claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 are rejected under 35 U.S.C. §101 as allegedly lacking utility.

Claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

Claims 10, 18, 23 and 32 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

(vii) Argument

I. Rejection on Grounds of Lack of Utility under 35 U.S.C. §101

Claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 are rejected under 35 U.S.C. §101 as allegedly lacking a well-established utility or a credible, substantial and specific asserted utility. The Examiner acknowledges that the claimed nucleic acids and their encoded hOCTN1 transporter polypeptides can be used to screen for and transport carcinostatic compounds, but asserts that these do not qualify as specific and substantial uses because, like the compounds and nucleic acids respectively at issue in the Brenner (*Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct. 1966)) and Fisher (*In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005)) cases, "further research is required to identify or reasonably confirm a specific and substantial utility." According to the Advisory Action, "Although the hOCTN1 protein of the instant application is able to transport carcinostatics, the physiological function of the protein has yet to be determined."

A. The Asserted Utility is Specific, Substantial and Credible

Appellant pointed out in the Amendment after Final that the specification discloses use of the hOCTN1 transporter protein encoded by the presently claimed nucleic acids in a screen for carcinostatic compounds transported by the protein. The Advisory Action acknowledges that the specification discloses such a use, but maintains that "**screening for carcinostatics is not specific or substantial. Such assays can be performed with any polypeptide. The specification discloses nothing specific or substantial for the compounds screened in this method.**" The Examiner's position is not understood.

First, Appellants point out the rather obvious fact that, by definition, carcinostatic compounds that are identified in a screen with hOCTN1 transporter protein have the specific and substantial use of being carcinostatic compounds (i.e., able to inhibit growth of cancerous cells). It is not clear why the Examiner believes otherwise.

Second, Appellants are mystified as to why the Examiner asserts that "**Such assays can be performed with any polypeptide.**" No explanation is provided as to why anyone would wish to perform such an assay with "any" polypeptide, including those that do not possess transporter activity. Perhaps it is theoretically possible to attempt to perform *any* assay with *any*

polypeptide, but obviously most of such attempts with random polypeptides not previously identified as having a relevant activity would be doomed to failure. Appellant is not proposing some random screening assay that is no more applicable to the presently claimed nucleic acids than to any others, and thus lacks specificity. Rather, Appellant's asserted utility is narrow and specific to the *particular* activity identified by Appellant for the presently claimed nucleic acids: transport of organic cations, including carcinostatic compounds. Appellant has demonstrated that hOCTN1 is able to transport organic cations, including some that are carcinostatic compounds. See, e.g., Examples 6 and 7. The Examiner does not dispute that hOCTN1 possesses this activity. Appellant has asserted that, because of this demonstrated activity, the presently claimed nucleic acids, vectors, and cells are useful in screening assays designed to develop new drugs that can be transported by hOCTN1 (see, e.g., page 31, lines 5-16, and page 35, lines 6-12). That a screen for anti-cancer drugs qualifies as a "substantial" utility is without serious question. That a screen for anti-cancer drugs that are transported by an organic cation transporter protein qualifies as a "specific" utility is also clear. These points are discussed in detail below.[1]

Specific Utility

The Office has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement," which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph ("Utility Guidelines"), and an "Overview of Legal Precedent Governing the Utility Requirement" ("Legal Overview") to support the Utility Guidelines. The Utility Guidelines define a "specific" utility as one that is particular to the subject matter claimed (just as in the present situation).

The Utility Guidelines provide an example of a nucleic acid with a "non-specific" utility as one where the asserted utility is that of a "gene probe," without specifying the gene target to which it can bind. This would be comparable to the present facts only if Appellant's specification has failed to say anything about hOCTN1 other than that it could be used in generic

[1] The Examiner has not challenged the credibility of the asserted utility, so that prong of the utility requirement is taken as established and will not be discussed here.

"drug screening", with no clue as to what sort of drug it would be capable of finding, or for what type of disease, or how the screen would be carried out.

This is far from being the case with regard to the instant claims. The specification clearly and extensively characterizes the structural features and biological activity of the newly discovered OCTN1 gene family. The teachings of the specification establish that this new gene family belongs to the general class of organic cation transporter proteins, several of which were known and previously studied in biological systems. Based on the teachings as a whole, the specification asserts a utility for the claimed isolated nucleic acids, namely, expressing the encoded hOCTN1 transporter proteins in cells and screening for carcinostatics that are preferentially absorbed and transported by hOCTN1. The screen permits the selection of carcinostatics that will preferentially be absorbed by target tissues or cells that express the hOCTN1 transporter. If one is trying to treat a cancer in which the cancerous cells express the hOCTN1 transporter, one can use the screen to determine whether a given known carcinostatic compound would be effectively taken up by those cells. Similarly, the screen can be used to identify new carcinostatic compounds that are preferentially absorbed and transported by hOCTN1, so are potentially useful for the same purpose. The specification asserts utility of the nucleic acids in expressing proteins that function as organic transporters of carcinostatic compounds, and illustrates this utility by showing that hOCTN1 actually transports known carcinostatins such as as actinomycin D, etoposide, vinblastine and daunomycin.

The asserted utility is therefore specific because it is particular to the type of protein, the hOCTN1 organic cation transporter, discovered by Appellant. Contrary to the Examiner's assertions, the screen is not broadly applicable to "any" protein. Rather, it is directly related to the disclosed function, that of an organic cation transporter, identified for the particular protein, hOCTN1, encoded by the claimed nucleic acids. Appellant has not merely hypothesized that the claimed nucleic acids and their encoded proteins "may be useful" in a general sense. See MPEP §2107.01. Rather, the specification teaches why these particular nucleic acids and their encoded proteins have specific uses, and then goes on to demonstrate the specific uses.

Substantial Utility

The MPEP, in discussing "substantial" utility at §2107.01, states that a "substantial utility" defines a "real world" use that does not require carrying out further research to identify or reasonably confirm the use. The Utility Guidelines provide an example of an insubstantial utility for a nucleic acid as one in which a claimed nucleic acid is used merely to study its own properties.

In this instance, the specification clearly meets the standard of providing a substantial utility. The specification teaches how the proteins encoded by the claimed nucleic acids can be used to study the transport of various organic cations, including carcinostatic agents, in cells, and can therefore be used to screen for compounds that are amenable to being transported by these proteins. The screening assays further find use in developing particular carcinostatic agents for treatment of different types of cancer, based on the expression of hOCTN1 in various tumor cell lines. No further research is necessary to confirm Appellant's identification and characterization of this gene as encoding organic cation transporter proteins, and indeed the Examiner does not challenge Appellant's characterization of hOCTN1 as an organic cation transporter. What is asserted as a utility is its use in assays to identify compounds (such as carcinostatic compounds) that are transported by hOCTN1, and so might be pharmacologically effective in certain diseases such as cancer. Thus, the asserted utility is substantial because it provides a significant, currently available, real-world benefit: an assay for finding the best cancer treatment for a cell or tissue that expresses the hOCTN1 transporter. The assay can select for the best treatment for a given patient's cancer from among several known carcinostatics, or can be used to find new carcinostatics. *There is no need to know anything more about the physiological role of hOCTN1 in order for the gene to be employed as disclosed.*

Distinguishing the *Brenner* and *Fisher* cases

The Examiner alleges in the Advisory Action that, unlike a scale or a microarray or a gas chromatograph, the claimed hOCTN1 nucleic acid molecules and their encoded polypeptides do not have patentable utility as "research tools" because "further research is required to identify or reasonably confirm a specific and substantial utility." The Examiner opines that the instant situation is analogous to the facts of *Brenner v. Manson,* 148 U.S.P.Q. 689 (Sup. Ct. 1966),

because, like the chemical compounds in *Brenner*, the claimed nucleic acids encoding organic cation transporter proteins allegedly have utility only in the broadest sense and not in an immediately obvious or fully disclosed "real world" utility. The Examiner also analogizes the instant case to *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005), alleging that, like the nucleic acids in the *Fisher* case, the instantly claimed nucleic acids do not have a "significant and presently available benefit to the public."

Appellant believes that the Office has misapplied those cases to the present situation, as the facts of the present case differ from those in *Brenner* and *Fisher* in key ways. For example, the specification in *Brenner* failed to assert any utility--or even any potential activity--for the compound produced by the claimed process. The Court rejected Brenner's argument that, since the compound could be used in research to determine whether it possessed a useful activity, the claimed process met the utility requirement. In distinct contrast to the facts of *Brenner*, Appellant's specification not only describes in great detail an asserted utility for the presently claimed nucleic acids, but also demonstrates that this utility indeed works. Furthermore, the utility disclose in the instant specification is not merely use in experiments to discover a possible use. The citation of *Brenner* in support of the rejection is therefore inapposite.

In *Fisher*, the court held that claims drawn to five expressed sequence tags (ESTs) from the maize genome did not have a specific or substantial utility because they were useful only to find the underlying genes whose identity and usefulness had yet to be determined. Unlike the situation in *Fisher*, hOCTN1's utility is not limited to figuring out the identity and usefulness of the claimed nucleic acids (or underlying genes) themselves. The instantly claimed isolated nucleic acids encode a fully sequenced, structurally- and functionally-characterized protein, hOCTN1. The specification actually demonstrates the utility of hOCTN1 in transporting known carcinostatic organic cation compounds. The asserted utility is specific because it applies only to organic cation transporters, and is substantial because it is immediately applicable in a current, real-world sense: to select optimal carcinostatics for uptake by cancer cells/tissues that express the hOCTN1 transporter.

In light of the above, Appellant submits that the asserted utility is specific, substantial, and credible.

"Physiological Role" and Utility

Despite the above arguments, the Examiner continues to insist that satisfaction of the utility requirement in the present case would require more information about the "physiological role" of hOCTN1 than was provided in the specification. According to the Advisory Action, "**There is no biological activity, phenotype, disease or condition, binding partner, or any other specific feature that is disclosed as being associated with OCTN1.**" Appellant has pointed out repeatedly that a biological activity (organic cation transport) is disclosed throughout the specification for OCTN1, and further that a useful screening assay that exploits that activity is also disclosed, and in fact *demonstrated* in the Examples. The Examiner dismisses this evidence of utility, apparently on the belief that the claimed nucleic acid would not be deemed useful by those of ordinary skill in the art unless the specification discloses what organic cations are naturally transported by the protein *in vivo* (i.e., the "physiological role" or "binding partner" of OCTN1), and/or some sort of differential expression in diseased cells versus normal cells to indicate an association of OCTN1 with a particular disease.[2] Appellant maintains that the Examiner has set a standard for the utility requirement that is nowhere in the law. Although the categories of information mentioned in the Advisory Action might well be useful in some situations to establish that a given nucleic acid meets the utility requirement, there is no basis in law to suppose that such information is absolutely required. Neither the statute nor the caselaw regarding the utility requirement, nor even the Utility Guidelines, sets forth such a standard. In the present case, Appellant has unequivocally demonstrated utility of the claimed nucleic acids, vectors and cells in an assay that is *specific* to organic cation transporters and is *substantial* in that it is a "real world" use. Nothing more should be required.

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[2] During a telephonic interview with Appellant's undersigned representative on January 10, 2008, the Examiner attempted to justify her assertions regarding the utility requirement by saying that there were several recent unpublished decisions by the Board of Patent Appeals and Interferences (BPAI) that stood for this proposition. Because the Examiner was unable to name any of those decisions, Appellant reviewed several recent BPAI decisions that concerned rejections of newly discovered proteins or nucleic acids for lack of utility. The ones that appeared to Appellant to be most relevant to the present rejection were discussed in the Amendment after Final, where Appellant distinguished each from the present facts. In response, the Advisory Action explained that the rejection was not based on these non-precedential opinions of the Board, but rather on the statute. Appellant reiterates that neither the statute nor the *Brenner* and *Fisher* cases cited by the Examiner nor any of the non-precedential BPAI decisions that Appellant could locate supports the rejection of the present claims for lack of utility.

It may be helpful to analogize the present situation to a hypothetical discovery of a compound extracted from the bark of a tree and disclosed in the specification to be useful as a starting material for synthesis of related compounds having potent anticancer activity against tumors in animals. In this hypothetical fact pattern, nothing is known about the physiological role the compound performs in the tree, nor is there any link to a known disease of the tree. The asserted utility is as a starting material for synthesis of anticancer agents, a utility that may have nothing to do with its physiological role in the tree. There is no question that this hypothetical compound would be found to have patentable utility despite the lack of information about its physiological role. Similarly, the utility of the presently claimed nucleic acids and their encoded proteins disclosed in the specification does not hinge on knowledge of their "physiological role," nor on any association with a disease.

B. Well-established Utility

Appellant further submits that use of hOCTN1 in a screening assay is also a "well-established" utility, *i.e.*, even had it not been explicitly asserted in the specification, it nonetheless would have satisfied the utility requirement. This point was made in the Amendment after Final, but was not even addressed in the Advisory Action. As the references provided with the attached Appendix show, long before the instant application's earliest priority date, the distinct structural features that characterized organic cation transporter proteins[3] and their role in drug uptake and distribution in organs such as intestines,[4] kidneys,[5] and the liver[6] were well-known. Thus, regardless of what utilities are or are not asserted in the specification, the claimed isolated nucleic acids and vectors encode proteins that have a well-established utility, *i.e.*, one of ordinary skill in the art would immediately appreciate why the hOCTN1

[3] See, Maiden *et al.*, *Nature*, 325:641-643 (1987), which was made of record in this case with the Amendment after Final and is included in the Evidence Appendix as Exhibit A.

[4] See, Tsuji *et al.*, *Pharm. Res.* 13(7):963-1132 (1996), which was made of record in this case with the Amendment after Final and is included in the Evidence Appendix as Exhibit B.

[5] See, Ullrich *et al.*, *Clin. Investig.* 71:843-848 (1993), which was made of record in this case with the Amendment after Final and is included in the Evidence Appendix as Exhibit C.

[6] See, Meijer *et al.*, *J. Pharmacokin. Biopharm.*, 18:35-70 (1990), which was made of record in this case with the Amendment after Final and is included in the Evidence Appendix as Exhibit D.

protein is useful, based on disclosed structural and functional characteristics that establish its role as an organic cation transporter.

C. Claim-by-claim Analysis

Appellant understands the Examiner's rejection to apply equally to all of the pending claims, regardless of breadth and regardless of whether the claim is drawn to a nucleic acid, a vector, a host cell, or a method of producing a polypeptide. The arguments set forth above fully counter the rejection for lack of utility as formulated in the Office actions and Advisory Actions of record. If the Board chooses to maintain the rejection but formulate the rejection differently than did the Examiner (e.g., by finding only the broader claims, such as claims 10 and 11, to lack utility on some sort of grounds not applicable to the narrower claims, or *vice versa*), Appellant requests the opportunity to address that differently formulated rejection in re-opened prosecution.

Claims 8, 11, 13, and 36 are drawn to isolated nucleic acids. Each of these claims broadly encompasses SEQ ID NO:2, the cDNA sequence encoding SEQ ID NO:1 (hOCTN1). SEQ ID NO:2 could be used as a template to generate the complement of SEQ ID NO:2, which would possess the well-established utility of being useful as a probe to detect expression of hOCTN1 in a given patient's cancer cells, e.g., in Northern analysis as described in Examples 3 and 5. One could use the knowledge that hOCTN1 is or is not expressed in a patient's cancer cells to determine whether treatment with a particular organic cation carcinostatic compound would be worthwhile. If hOCTN1 is found to be expressed in the cancer cells, one would then select an organic cation carcinostatic compound that had been shown (in assays disclosed in the specification) to be transported by hOCTN1. Thus, these claims possess a utility in addition to the one discussed above that applies to all of the claims.

The nucleic acids of claims 8, 10, 11, 13, 32, and 36 and the vectors of claims 16, 18, and 19 are useful for producing the cultured host cells of claims 21, 23, 24, and 25. Those host cells can be used to express hOCTN1 polypeptide or a variant thereof, which in turn can be used to generate antibodies specific for hOCTN1 polypeptide (see, e.g., the specification at pages 7-8). The antibodies are useful to determine whether a given patient's cancer cells are expressing hOCTN1, and so can allow a physician to decide whether treatment with a particular organic

cation carcinostatic compound known to be transported by hOCTN1 would be worthwhile (as described above).

Accordingly, there are multiple bases for finding that the present claims possess utility under 35 USC § 101. In view of the above, Appellant submits that the utility requirement is more than amply met in this case. Reversal of the rejection of all of the claims for lack of utility is respectfully requested.

II. Rejection for Lack of Enablement under 35 U.S.C. §112, first paragraph

Claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Advisory Action opines that, since the claims are allegedly not supported by either a specific and substantial asserted utility or a well-established utility, one of skill in the art would not know how to make and use what is claimed.

Appellant submits that the above arguments addressing the utility requirement establish that the specification at the time of filing clearly taught how to make and use the claimed isolated nucleic acids in assays where the encoded hOCTN1 protein is expressed and screened for its ability to transport a variety of organic cations, including carcinostatic compounds. The transport activity is demonstrated in several working examples (Examples 6-8, for instance), and also is consistent with the structural information provided in the specification (e.g., in Example 2 at pages 22-23). The disclosures in the specification also enable one of ordinary skill in the art to use the claimed nucleic acids, vectors, and/or cells to make probes and/or antibodies that can be used to determine whether a patient's cancer cells express hOCTN1, and so could be treated with a carcinostatic agent that is transported by hOCTN1. Appellant therefore requests reversal of the rejection for lack of enablement.

III. Rejection for Inadequate Written Description under 35 U.S.C. §112, first paragraph

The Advisory Action maintains the rejection of claims 10, 18, 23 and 32 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Advisory Action asserts that the specification does not describe which of the one to thirty

(claim 10) or one to ten (claim 32) amino acids of hOCTN1 can vary and still retain organic cation transporter function, and that "there is no description of the conserved regions that are critical to the structure and function of the genus claimed."

Claim 10 and dependent claims 18 and 23 encompass nucleic acids that encode a polypeptide having between one and thirty conservative amino acid substitutions in the hOCTN1 sequence. In the 551 amino acid sequence, this represents variants whose sequences are from 94.6% to 99.8% identical to the hOCTN1 SEQ ID NO:1 sequence, with all substitutions being conservative ones. Claim 32 is directed to nucleic acids that encode proteins containing even fewer substitutions (*i.e.*, one to ten conservative substitutions, corresponding to a sequence identity, compared to SEQ ID NO:1, of 98.1-99.8%).

The Examiner noted during the telephonic interview of January 10, 2008, that, if the sequence and function of a protein are described in the specification (which is certainly the case for hOCTN1), variants of the protein described as being 95% or more identical to the protein and retaining the activity of the protein are generally accepted as meeting the written description requirement. This principle was affirmed in the revised Written Description Training Materials, published by the Office on March 25, 2008. As Example 10 of the Training Materials notes, when the specification describes the sequence of a protein, those of skill in the art could recognize amino acid sequences that are least 95% identical to that of the protein. This is true regardless of whether the amino acid differences are conservative or random.

Claims 10, 18 and 23 encompass nucleic acids encoding proteins that are between 94.6% (30 substitutions) to 99.8% (one substitution) identical to the sequence of the hOCTN1 protein, and all substitutions must be conservative ones. Thus, nearly all of the variants encompassed by these claims are well within the 95% variance blessed by Example 10 of the revised Written Description Training Materials. The fact that all of the substitutions must be conservative ones further limits the genus and so strengthens Appellant's position with respect to these three claims even more. Claim 32 narrows the genus down to no more than 10 conservative substitutions (i.e., at least 98.1% identity to SEQ ID NO:1), so is well under the 95% limit blessed by the revised Written Description Training Materials. Appellant therefore submits that claims 10, 18, 23 and 32 easily satisfy the written description requirement.

The rejected claims also specify that the protein variants encoded by the nucleic acids are transporters of organic cations. The Examiner alleges that there is "no description" of the sites at which variability may be tolerated and there is "no information" regarding the correlation of structure and function. Appellant respectfully disagrees. The specification describes the characterization of several significant structural features/domains of the hOCTN1 protein. For example, Fig. 1 shows a hydrophobicity plot predicting the locations of several transmembrane domains; this is discussed further at page 22, lines 11-16. A transporter consensus sequence within SEQ ID NO:2 is described at page 6, lines 6-23, as well as at page 22, lines 16-26. A second consensus sequence is described at page 23, lines 1-14; this one is a putative ATP/GTP binding site, said to be typical for the so-called "ATP Binding Cassette type transporter" protein. The specification at page 22, lines 26-31, discloses that the sequence of hOCTN1 has four putative N-linked glycosylation sites and five putative protein kinase C phosphorylation sites, and says exactly where these sites are located in the sequence. Furthermore, the specification discloses the sequence of both the human and mouse OCTN1 proteins, enabling one of ordinary skill to align the two sequences and readily see which positions vary between the two homologs. Those non-conserved positions are presumptively able to tolerate change from the human OCTN1 sequence, particularly where the changes are all conservative substitutions. Given all of this disclosure, Appellant does not understand why the Advisory Action asserts, "**There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function.**" The Examiner plainly has not taken into account the substantial amount of such description in the specification. Given the modest scope of claim 10, and the even narrower scope of claim 32, one of ordinary skill in the art would readily recognize that Appellant was in possession of the entire genus of nucleic acids encompassed by each of these claims and their dependents.

Reversal of the rejection of claims 10, 18, 23 and 32 for lack of written description is therefore solicited.

CONCLUSION

For the reasons set forth above, Appellant respectfully requests that all of the rejections of claims 8, 10, 11, 13, 16, 18-21, 23-25, 27, 32 and 36 be reversed.

An attached Claims Appendix (viii) contains a copy of the claims under appeal.

An Evidence Appendix (ix) refers to attached Exhibits A-D.

A Related Proceedings Appendix (x) is attached as required, but contains no subject matter.

No fees are believed to be due in connection with this filing, the fee for filing an Appeal Brief having been previously paid in connection with the filing of the original Appeal Brief filed October 27, 2008; however, if any fees are due please apply them, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0057002.

Respectfully submitted,

Date: March 24, 200

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(viii) Appendix of Claims

8. An isolated nucleic acid encoding a polypeptide comprising the sequence of SEQ ID NO:1.

10. An isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:1, with one to 30 conservative amino acid substitutions, wherein the polypeptide is a transporter of an organic cation.

11. An isolated nucleic acid that hybridizes under stringent conditions to a probe, wherein:

the sequence of the probe consists of the complement of SEQ ID NO:2;

the stringent conditions comprise hybridization at 68 °C followed by washing in 2 X SSC/0.1% SDS for 20 minutes at room temperature and twice in 0.1 X SSC/0.1% SDS for 20 minutes at 50 °C; and

the isolated nucleic acid encodes a polypeptide that is a transporter of an organic cation.

13. The nucleic acid of claim 11, wherein the amino acid sequence of the polypeptide comprises SEQ ID NO:1.

16. A vector comprising the nucleic acid of claim 8.

18. A vector comprising the nucleic acid of claim 10.

19. A vector comprising the nucleic acid of claim 11.

20. A vector comprising the nucleic acid of claim 13.

21. A cultured host cell comprising the nucleic acid of claim 8.

23. A cultured host cell comprising the nucleic acid of claim 10.

24. A cultured host cell comprising the nucleic acid of claim 11.

25. A cultured host cell comprising the nucleic acid of claim 13.

27. A method of producing a polypeptide, the method comprising isolating the polypeptide from the cultured host cell of claim 21.

32. The nucleic acid of claim 10, wherein the sequence of the encoded polypeptide comprises the amino acid sequence of SEQ ID NO:1, with up to 10 conservative amino acid substitutions.

36. An isolated nucleic acid encoding a polypeptide consisting of the sequence of SEQ ID NO:1.

(ix) Evidence Appendix

Exhibit A Maiden *et al.*, *Nature*, 325:641-643 (1987)

Exhibit B Meijer *et al.*, *J. Pharmacokin. Biopharm.*, 18:35-70 (1990)

Exhibit C Ullrich *et al.*, *Clin. Investig.* 71:843-848 (1993)

Exhibit D Tsuji *et al.*, *Pharm. Res.* 13(7):963-1132 (1996)

(x) Related Proceedings Appendix

There are no related proceedings.